Mechanistic modeling of metastasis: cancer at the organism scale

Sébastien Benzekry

Mechanistic modeling of metastasis: cancer at the organism scale

S. Benzekry
Inria Bordeaux Sud-Ouest

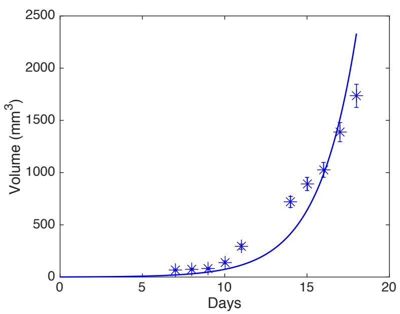
ISoP workshop
July 11th, 2019

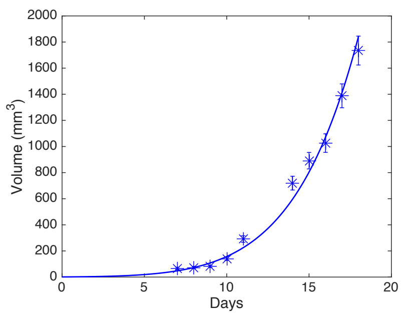
Modeling in ONCology

Can mathematical models be of help in oncology?

Understand (biology)

- **Theoretical** framework for description of the process
- Test different **hypotheses** and reject non-valid ones





Exponential

$$\frac{dV}{dt} = aV$$

Power law

$$\frac{dV}{dt} = aV^{\gamma}$$

Benzekry et al., PloS Comp Biol, 2014

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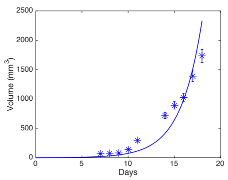
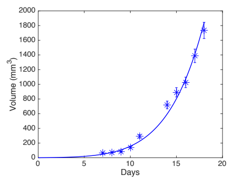


Exponential

$$\frac{dV}{dt} = aV$$

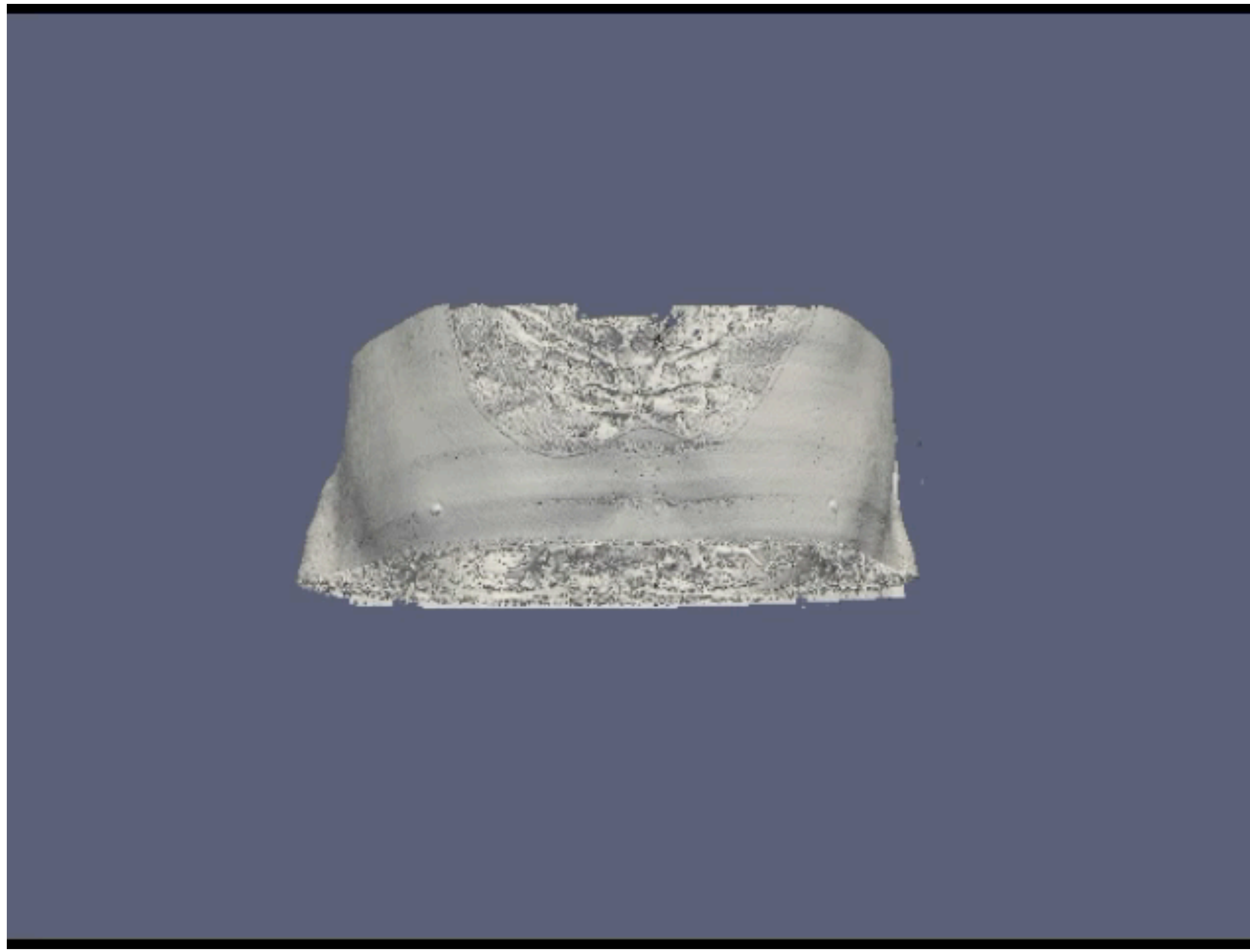


Power law

$$\frac{dV}{dt} = aV^{\gamma}$$

Predict and control (clinic)

- Predict tumor growth



Jouganous, Colin, Saut et al., 2014

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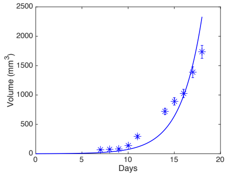

Exponential

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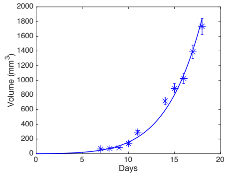
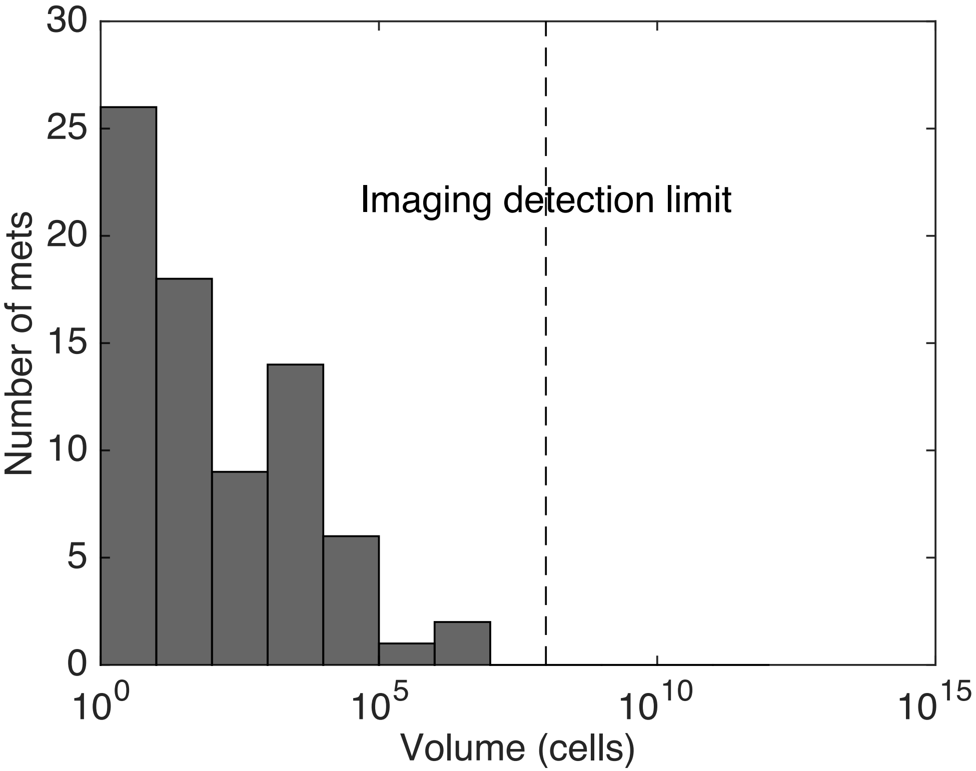


Power law

$$\frac{dV}{dt} = aV^{\gamma}$$

Predict and control (clinic)

- Predict **metastasis**
- **Personalize** (adjuvant) therapy



Benzekry et al., Cancer Res, 2016

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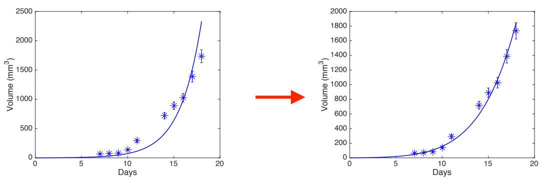
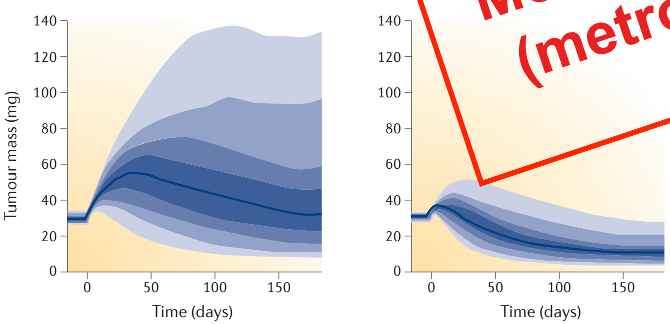


Exponential

Power law

Efficacy

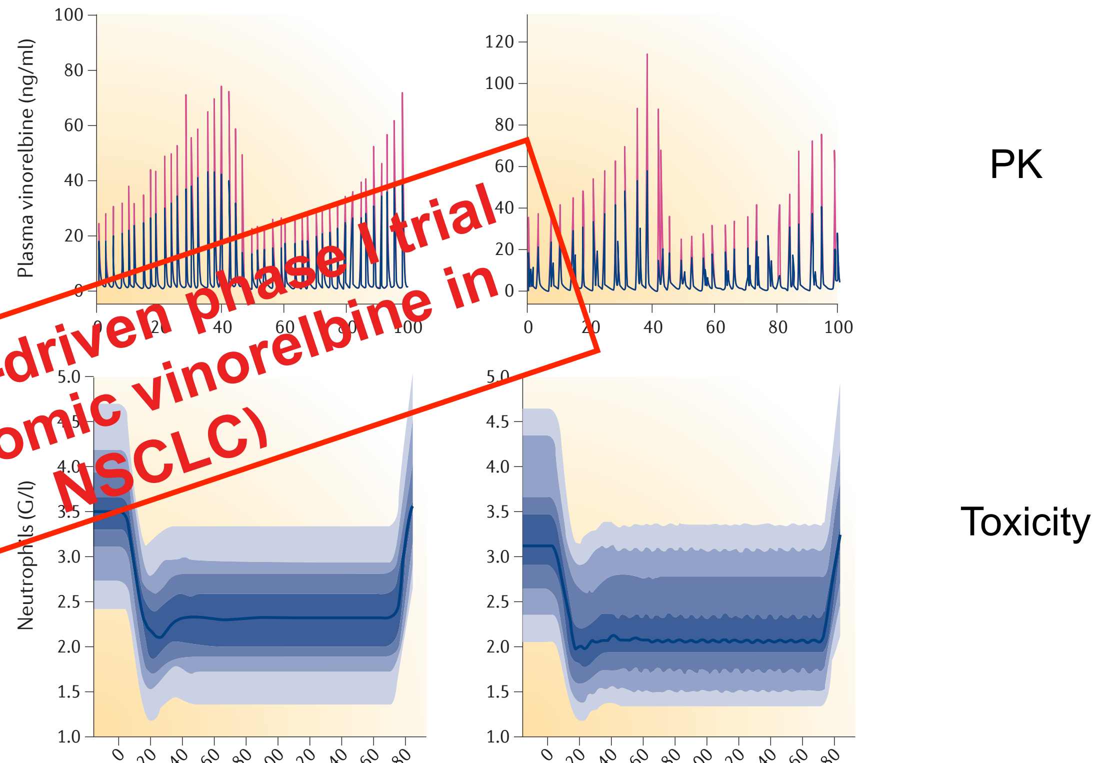


Predict and control (clinic)

- Rational and individual design of **drug regimen**

Empirical dosing
D1-D3-D5 50 mg

Model-based dosing
D1-D2-D4 60-30-60 mg



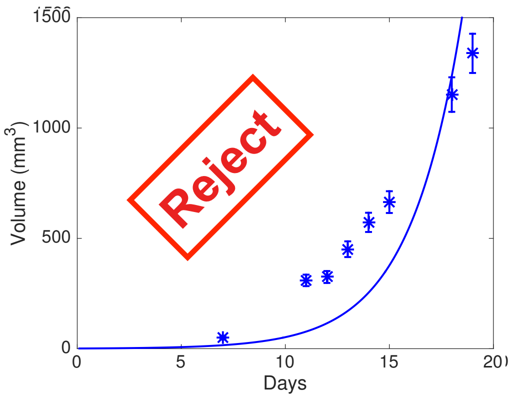
Barbolosi et al., Nat Rev Clin Onco., 2015

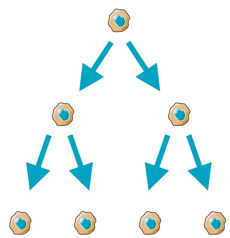
Tumor growth

Tumor growth

What are **minimal** biological processes able to recover the **kinetics** of (experimental) tumor growth?

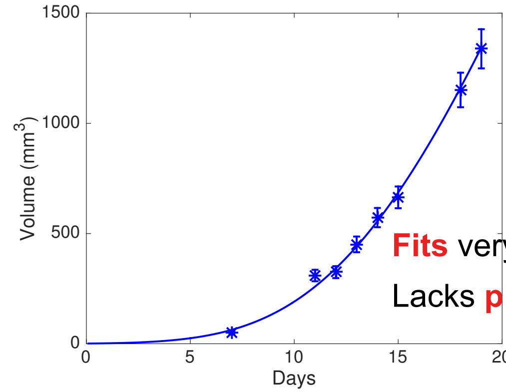
Exponential





$$\frac{dV}{dt} = aV$$

Gompertz

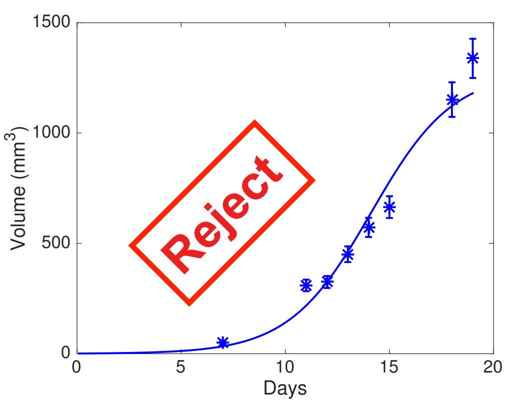


$$\frac{dV}{dt} = \alpha e^{-\beta t} V$$

Fits very well

Lacks **physiological** interpretation

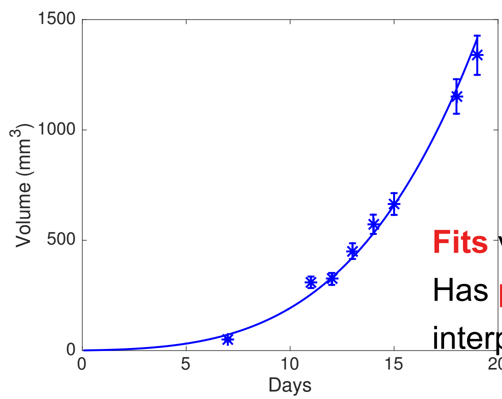
Logistic



Competition

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$$

Power law



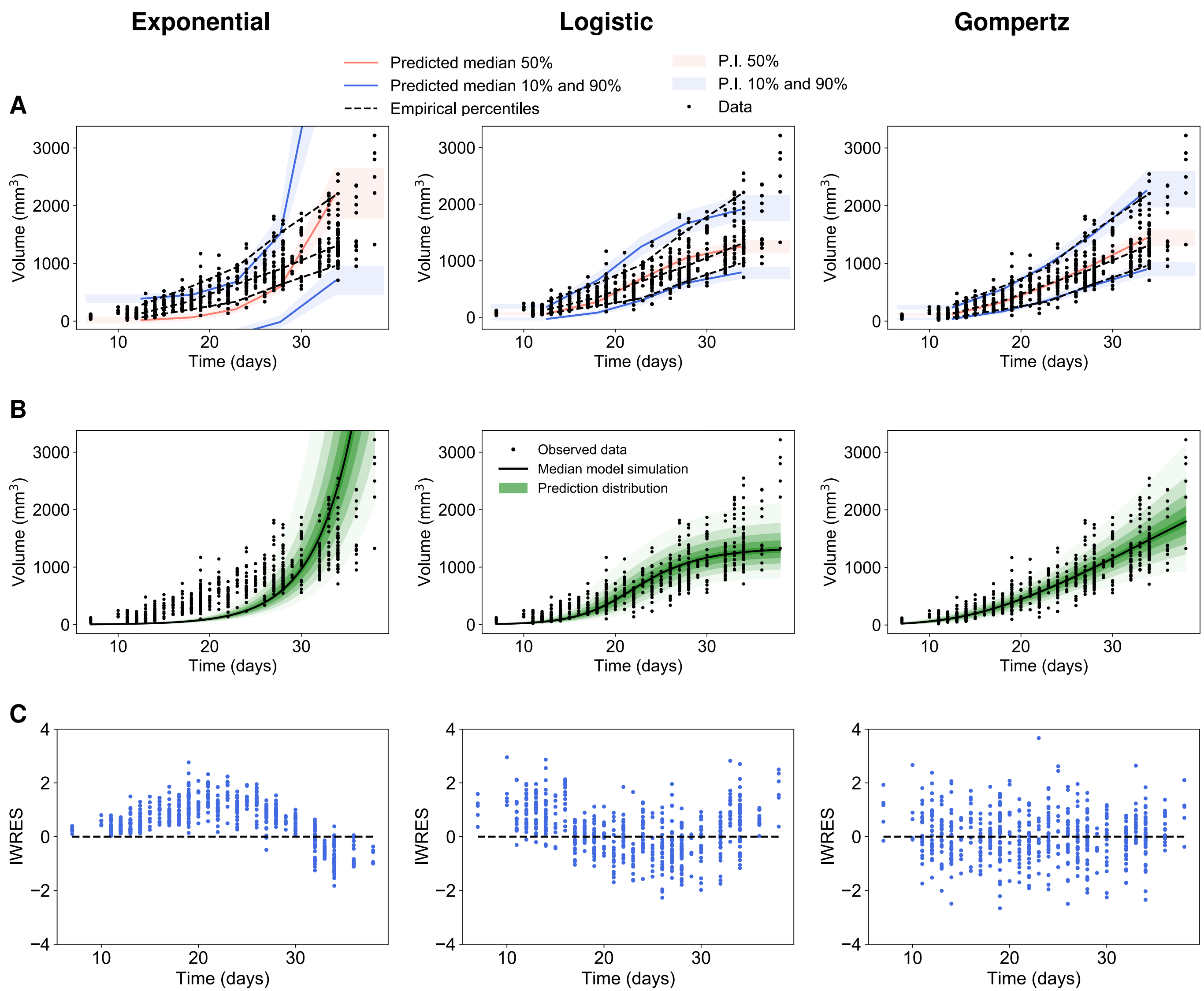
$$\frac{dV}{dt} = \alpha V^{\gamma}$$

Fits very well

Has **physiological** interpretation

Benzekry et al., PloS Comp Biol, 2014

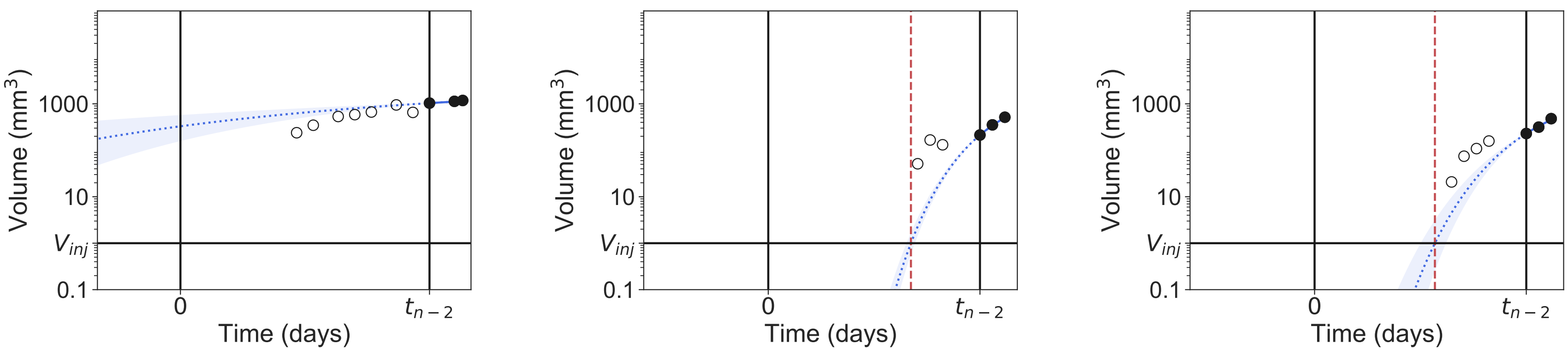
Population fit of tumor growth models



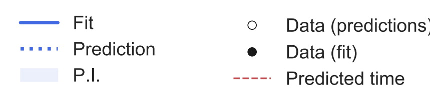
Vaghi et al. (Benzekry), bioRxiv, 2019

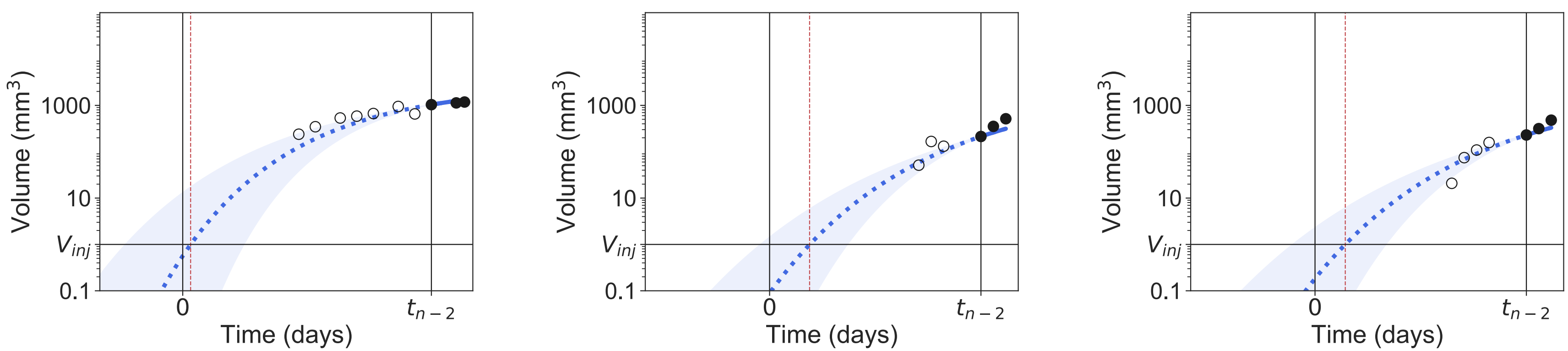
Bayesian estimation for prediction of tumor age

No a priori (MLE)



With a priori (Bayesian)



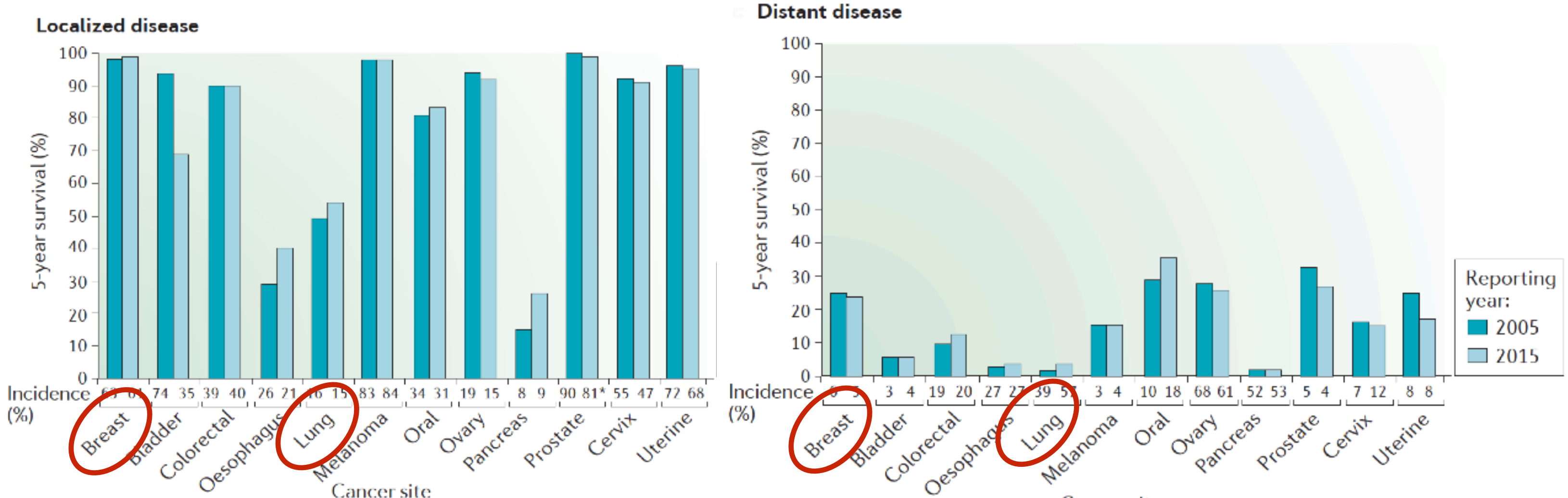


Vaghi et al. (Benzekry), bioRxiv, 2019

Metastasis

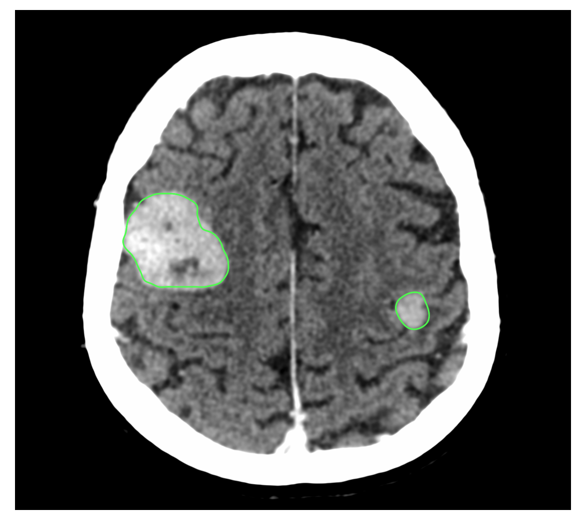
Metastasis (μετά = beyond, στάσιζ = place)

- Metastases are the **main cause of death** (>90%) from solid cancers *Lambert and Weinberg, Cell, 2017*



Steeg, Nat. Rev. Cancer, 2016

- **Breast**
  - 94% of cases are local or regional at diagnosis but 30% will relapse *Pollard, N Eng J Med, 2016*
  - Estimate the amount of **residual distant disease** at diagnosis in order to **personalize** the adjuvant (chemo)-therapy
  - Avoid heavy **toxicities** for low risk patients
- **Lung**
  - 57% of cases are metastatic
  - Decide whether to use **whole brain radiation therapy** or just (stereotactic) surgery
  - Avoid cognitive impairment of the patient



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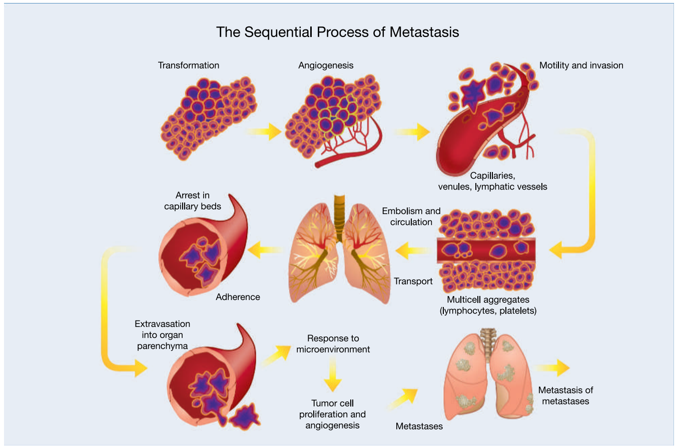
Some biological questions of interest to mathematical modeling

- **Minimal** model of metastatic dissemination and colonization able to reproduce the **systemic dynamics** of a solid cancer disease

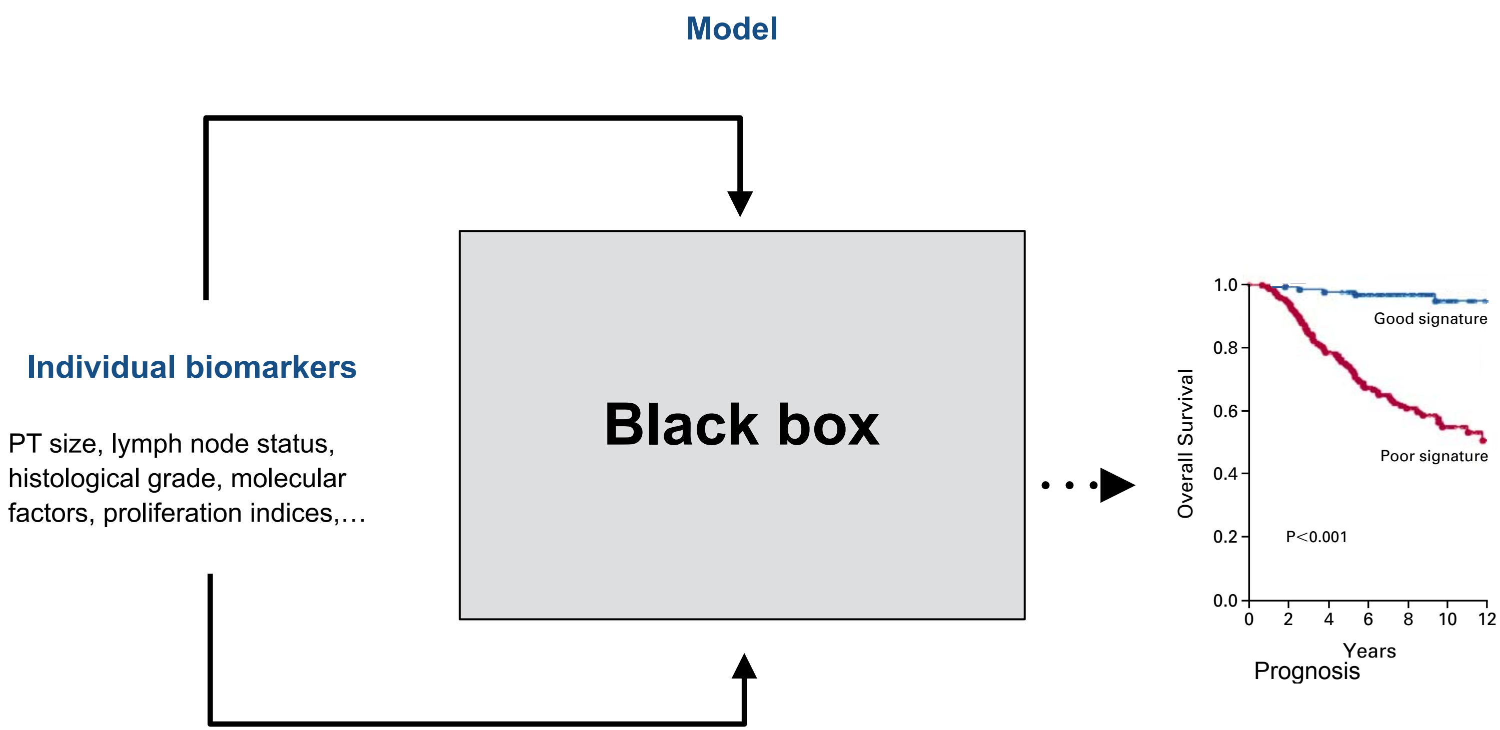
- Investigate the relevance of several processes:
  - (early VS late event *Klein, Nat Rev Cancer, 2009*)
  - (metastases of metastases *Gundem et al., Nature, 2015*)
  - (dormancy *Chambers and Groom, Nat Rev Cancer, 2002*)
  - **tumor-tumor interactions**
  - (cancer-immune interactions)
  - **differential effect of therapy** *Ebos et al. (Kerbel), Cancer Cell, 2009*
  - ((pre-)metastatic niche *Peinado et al. (Lyden), Nature, 2005*)
  - systemic inhibition of angiogenesis *O'Reilly et al. (Folkman), Cell, 1990s*
  - (self-seeding *Norton, Nat Med, 2001*)



Talmadge and Fidler, Cancer Res, 2010

Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) **tumor growth**
- Existing models are based on a statistical, **biologically agnostic**, prediction of survival



Metastasis: a forgotten major player in modeling

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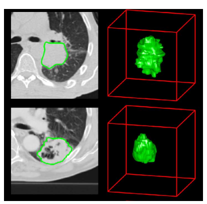
- Existing models are based on a statistical, **biologically agnostic**, prediction of survival

Clinical data

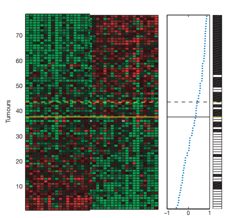
PT size, lymph node status, histological grade, molecular factors, proliferation indices,…

Imaging data (Radiomics)



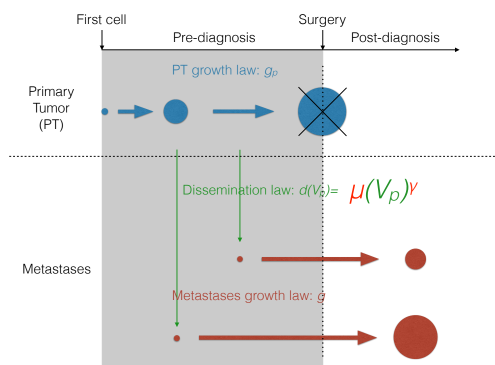
Aerts et al., Nat Commun, 2014

Molecular data (-omics)



van't Veer et al., Nature, 2002

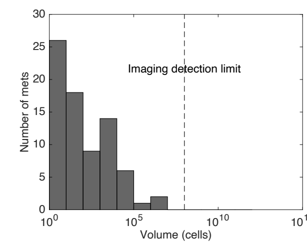
Biologically-based model



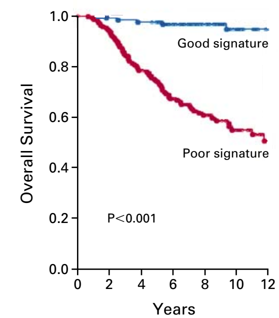
$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p))\, V_p$$

$$\begin{cases} \partial_t \rho(t,v) + \partial_v \left((\alpha - \beta \ln(v))\, v \rho(t,v) \right) = 0 \\ g(V_0)\rho(t,V_0) = \mu V_p(t)^\gamma \\ \rho(0,v) = 0 \end{cases}$$

Prediction

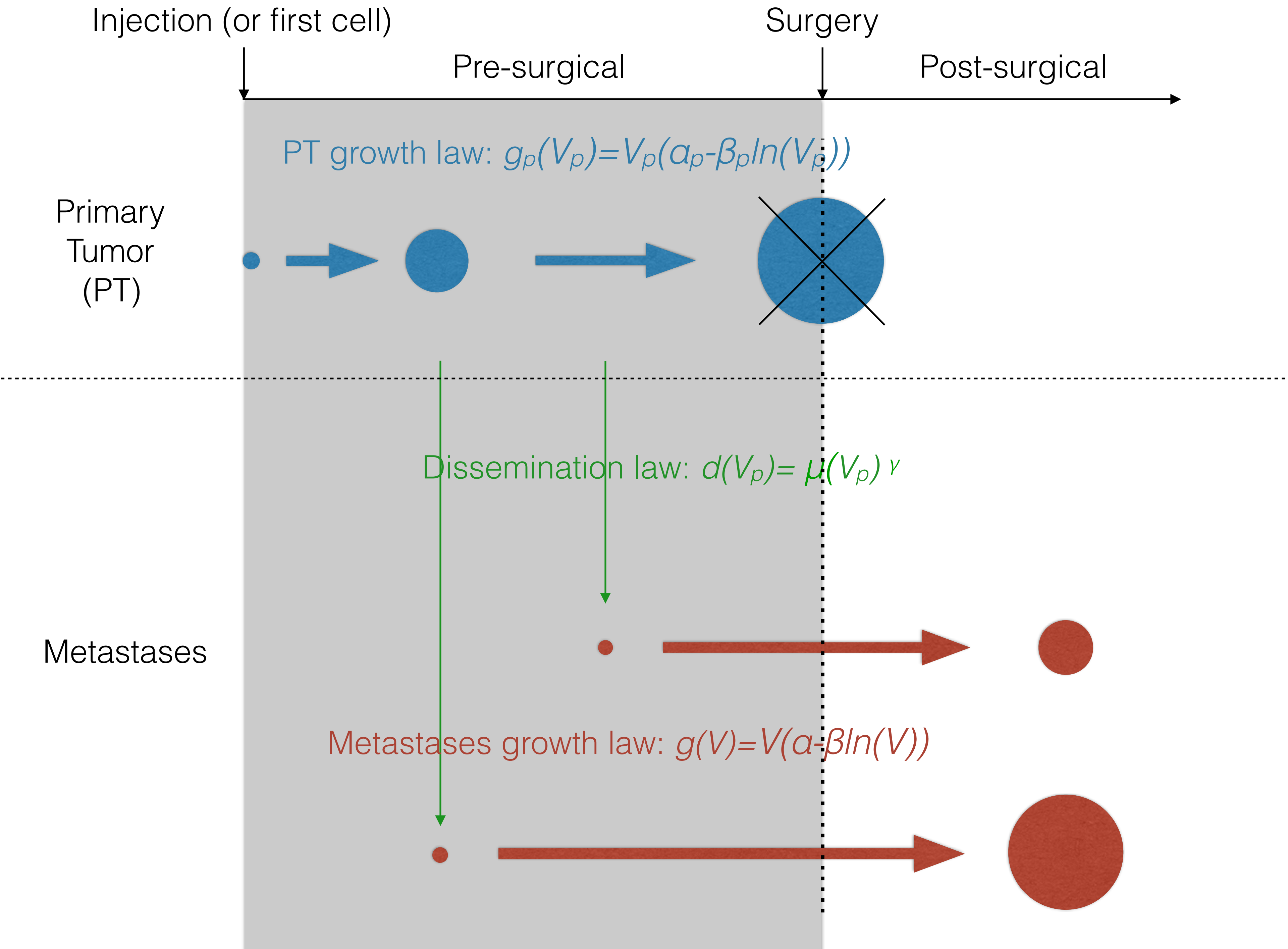


Diagnosis



Prognosis

Simulation and individualization of therapy


Injection (or first cell)
Surgery
Pre-surgical
Post-surgical
PT growth law: $g_p(V_p)=V_p(\alpha_p-\beta_p ln(V_p))$
Primary Tumor (PT)
Dissemination law: $d(V_p)= \mu(V_p)^{\gamma}$
Metastases
Metastases growth law: $g(V)=V(\alpha-\beta ln(V))$

Mathematical formalism

- Primary tumor V_p grows with rate g_p [size.day^{-1}]

$$\frac{dV_p}{dt} = \mathbf{g_p(V_p)}, \quad V_p(t=0) = V_i$$

- **Population** of metastases represented by a **density** ***ρ(t,v)*** [size^{-1}] structured in **size *v***

- Secondary tumors grow in size with rate *g(v)*

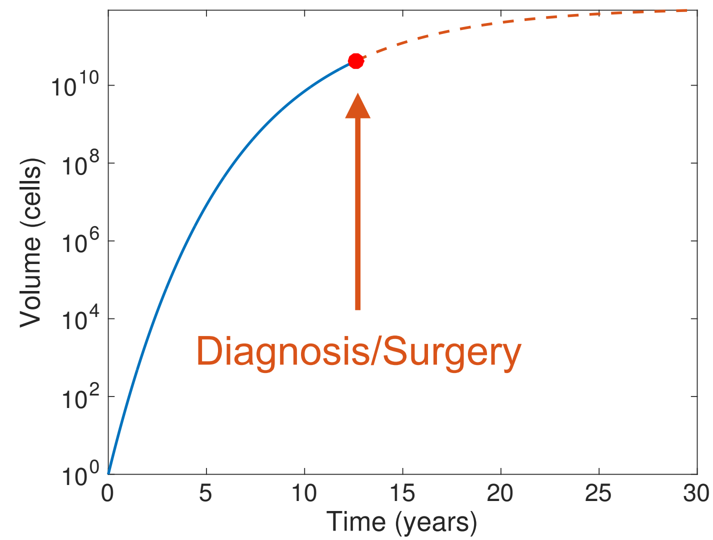
$$\partial_t \rho(t,v) + \partial_v (g(v)\rho(t,v)) = 0$$

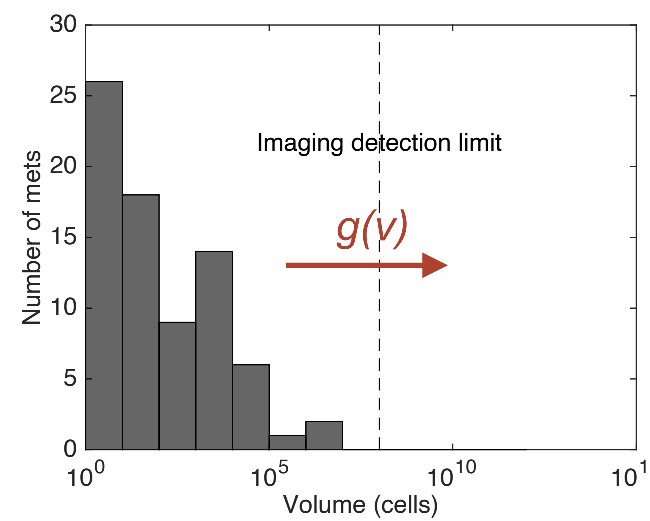
- They are spread by the PT with **dissemination rate** *d(V$_p$(t))* [day^{-1}]

$$g(V_0)\rho(t,V_0) = d(V_p(t))\left(+\int_{V_0}^{+\infty} d(v)\rho(t,v)dv\right)$$

→ fast computation of the metastatic burden

$$M(t) = \int_{V_0}^{+\infty} v\rho(t,v)dv = \int_0^t d\left(V_p(t-s)\right)V(s)ds$$



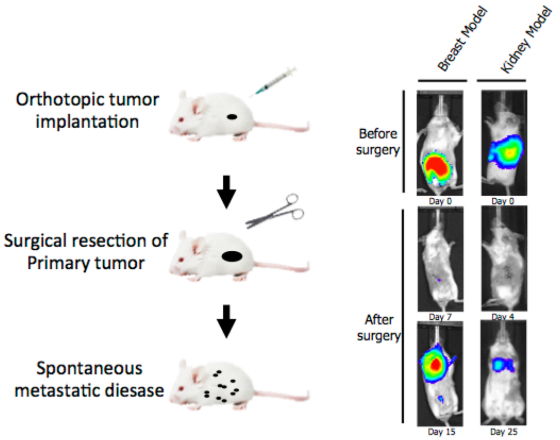


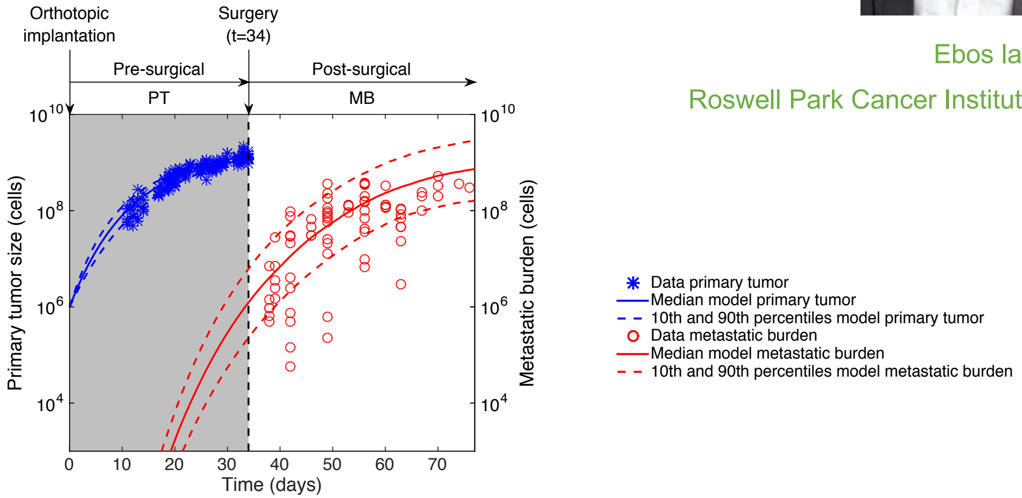
Iwata, Kawasaki, Shigesada, J Theor Biol, 2000

Validation on animal data

Ebos lab

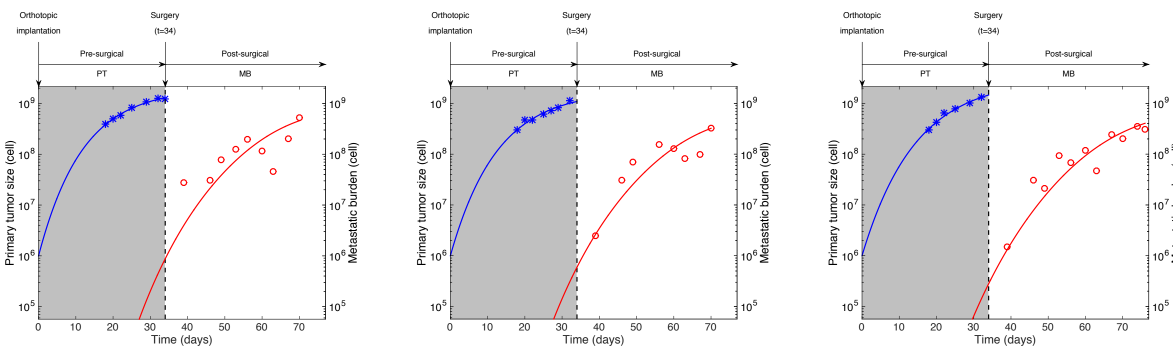
Roswell Park Cancer Institute





Nonlinear **mixed-effects** statistical model for inter-animal variability

$$\theta^i = \theta_{pop} + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$



$\Longrightarrow$ **same growth** for PT and mets: $\alpha_p = \alpha$, $\beta_p = \beta$

Benzekry et al. (Ebos), Cancer Res, 2016

Differential effects of anti-angiogenic therapies between primary tumor and metastases

Cell PRESS
Cancer Cell
Report

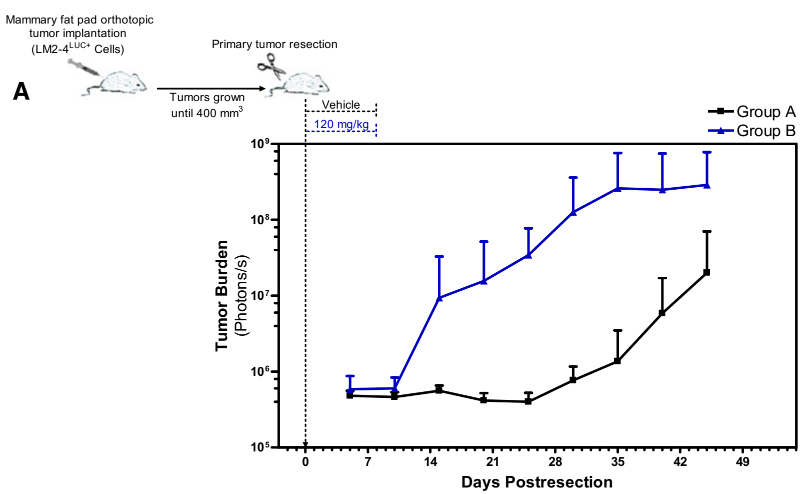
Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

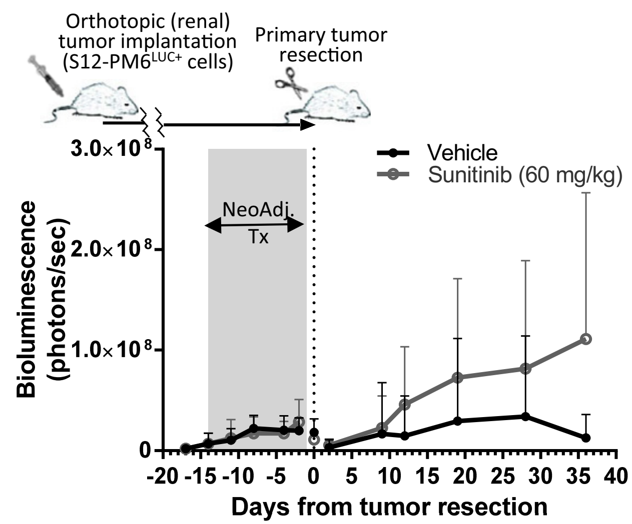
John M.L. Ebos,[1,2] Christina R. Lee,[1] William Cruz-Munoz,[1] Georg A. Bjarnason,[3] James G. Christensen,[4] and Robert S. Kerbel[1,2,*]

Published online: October 31, 2014
Research Article
TRANSPARENT PROCESS
OPEN ACCESS
EMBO Molecular Medicine

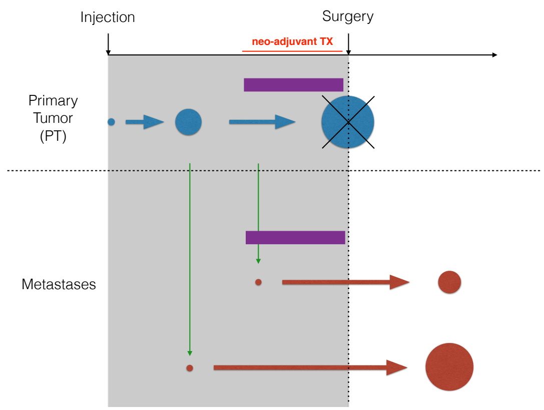
Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy

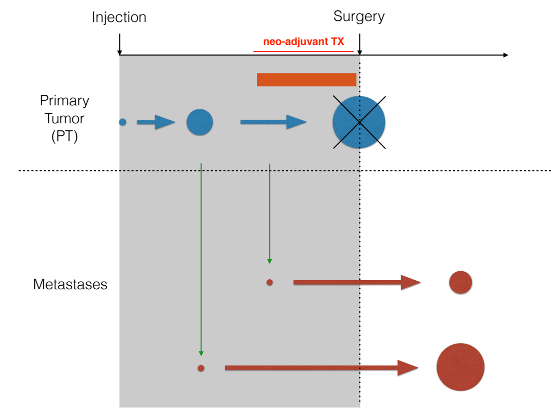
John M L Ebos[1,*], Michalis Mastri[1], Christina R Lee[2], Amanda Tracz[1], John M Hudson[2], Kristopher Attwood[3], William R Cruz-Munoz[2], Christopher Jedeszko[2], Peter Burns[2,4] & Robert S Kerbel[2,4]



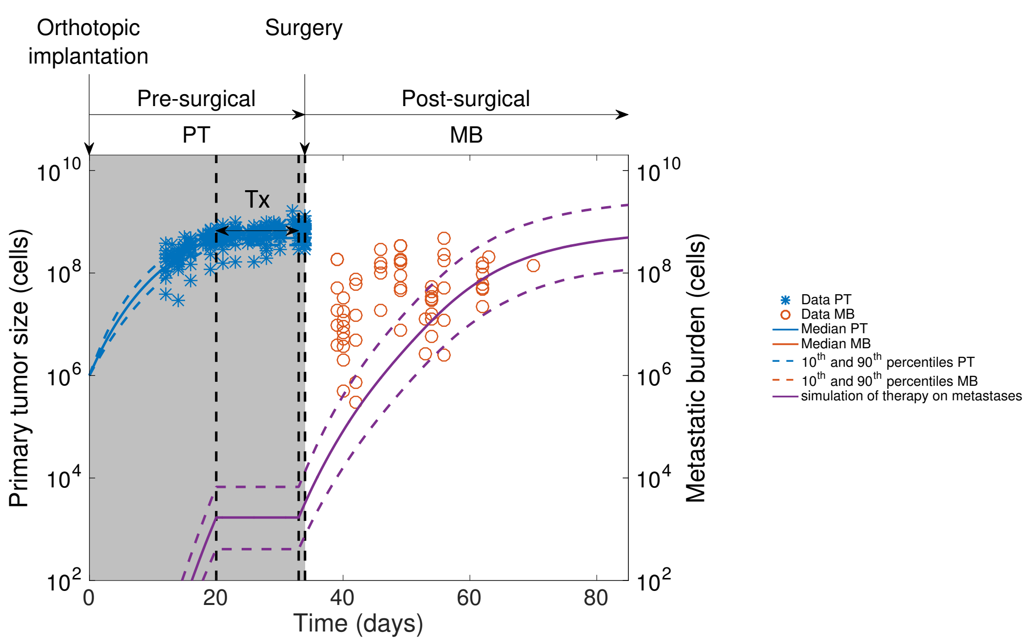


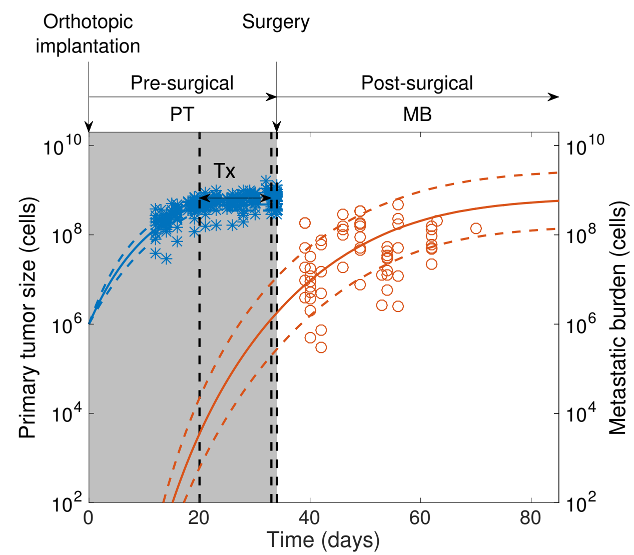
Testing hypotheses for neo-adjuvant TKI effect





or

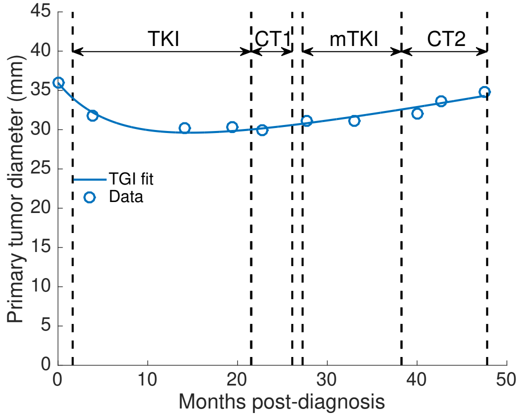




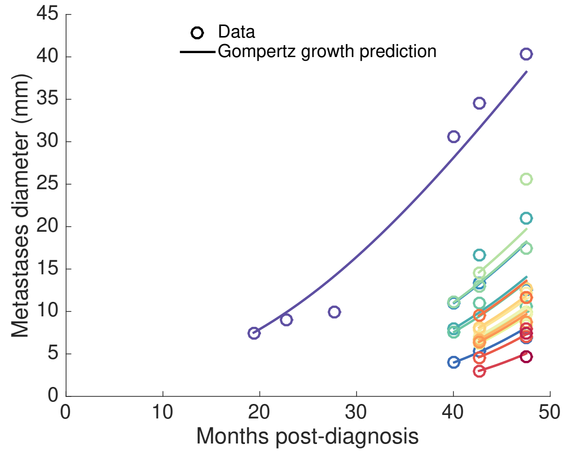
Clinical application - Brain Metastasis from NSCLC

Data of a NSCLC patient with brain mets

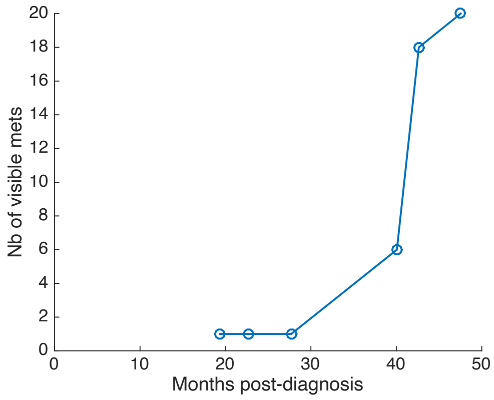
Primary tumor size



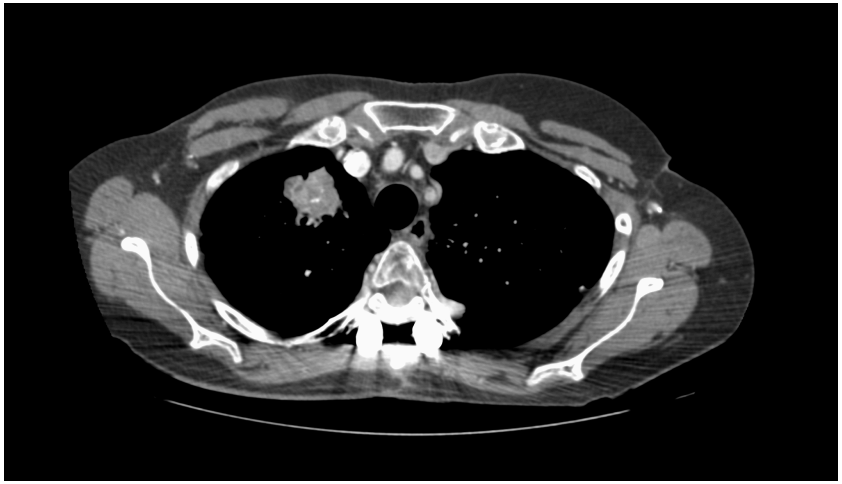
Metastases size



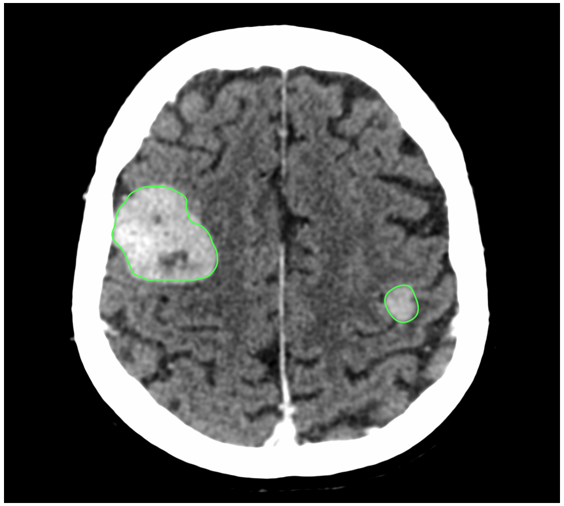
Number of visible mets



Lung CT



Brain CT scan



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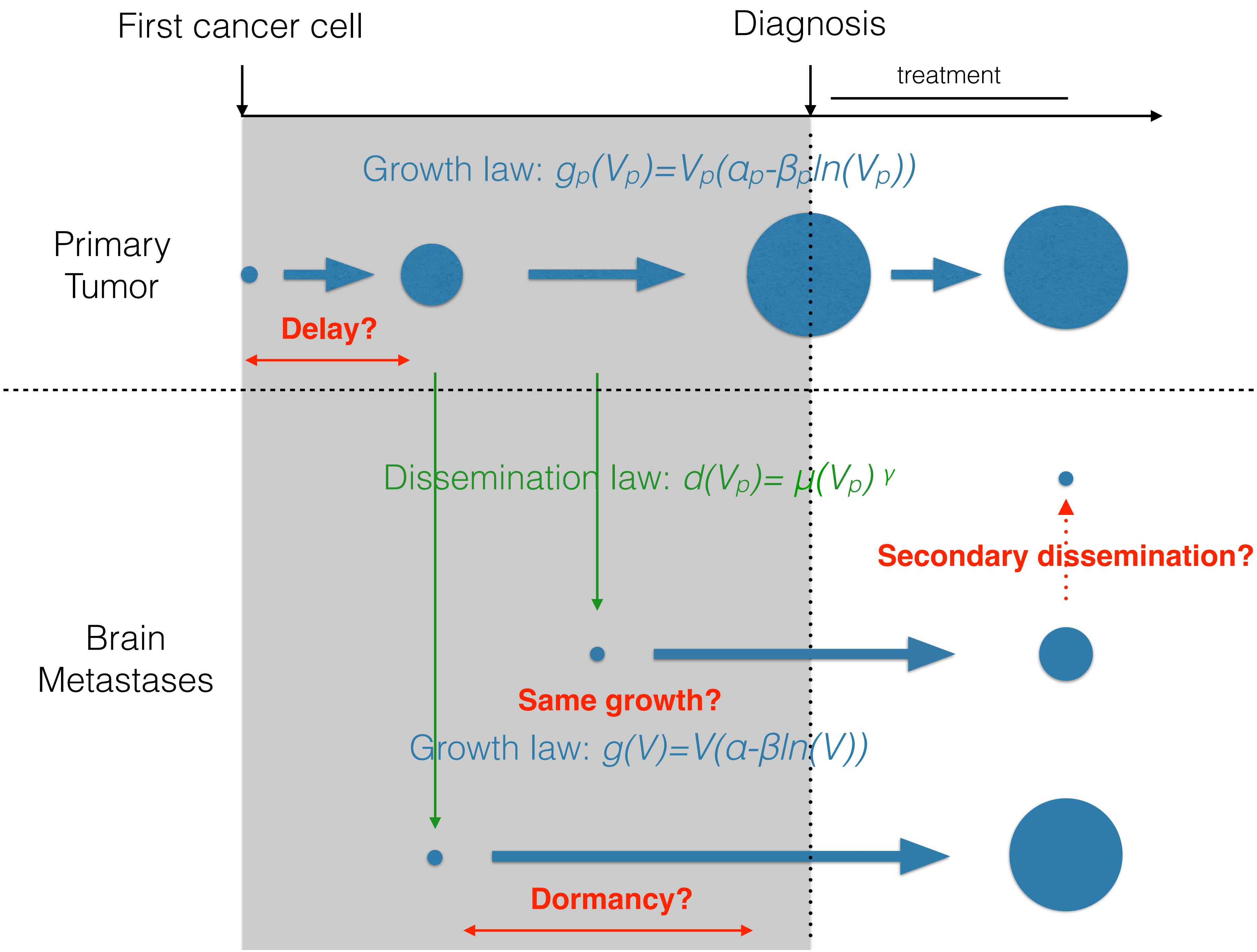
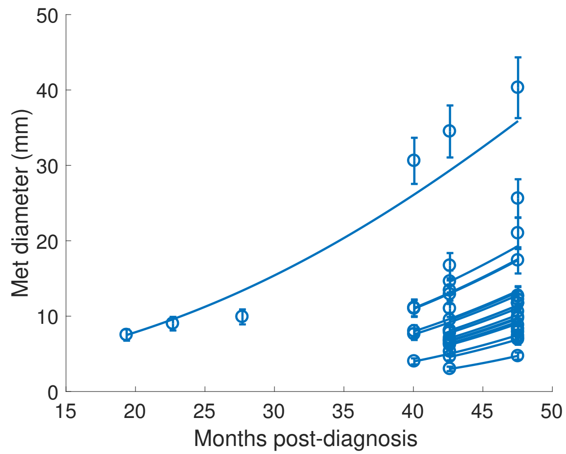
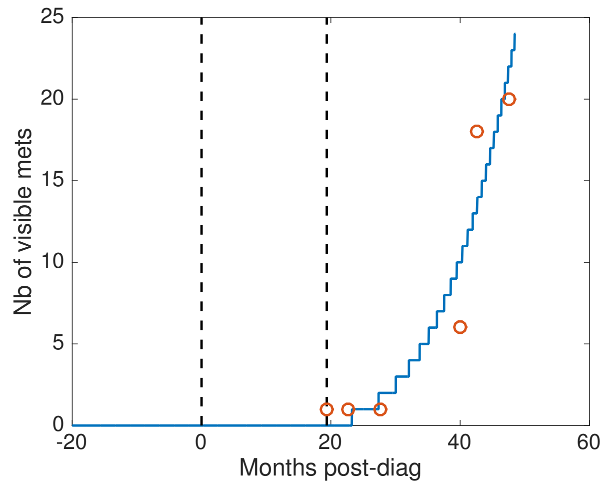

First cancel cell
Diagnosis
treatment
Growth law: $g_p(V_p)=V_p(\alpha_p-\beta_p ln(V_p))$
Primary Tumor
Delay?
Dissemination law: $d(V_p)= \mu(V_p)^{\gamma}$
Secondary dissemination?
Brain Metastases
Same growth?
Growth law: $g(V)=V(\alpha-\beta ln(V))$
Dormancy?

The model with dormancy could describe best the data

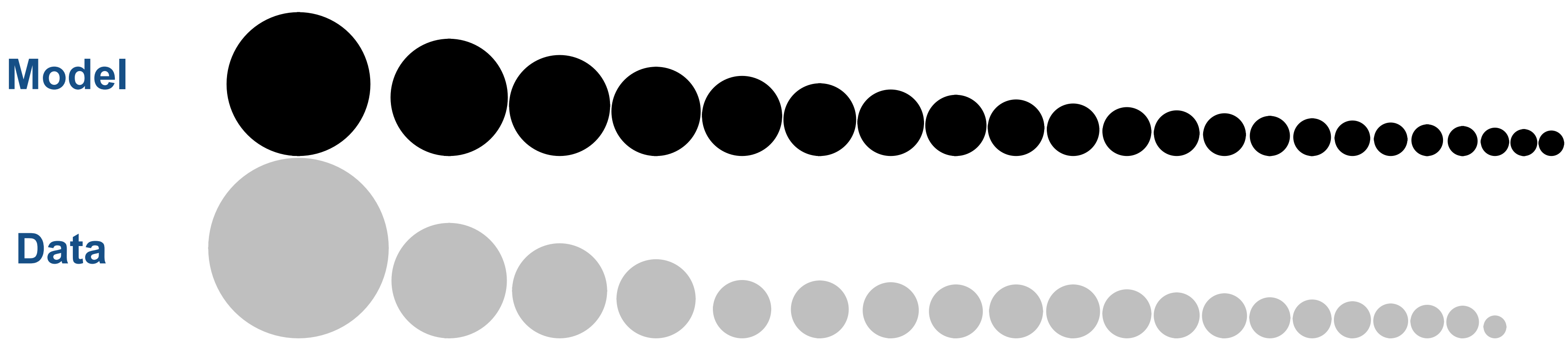




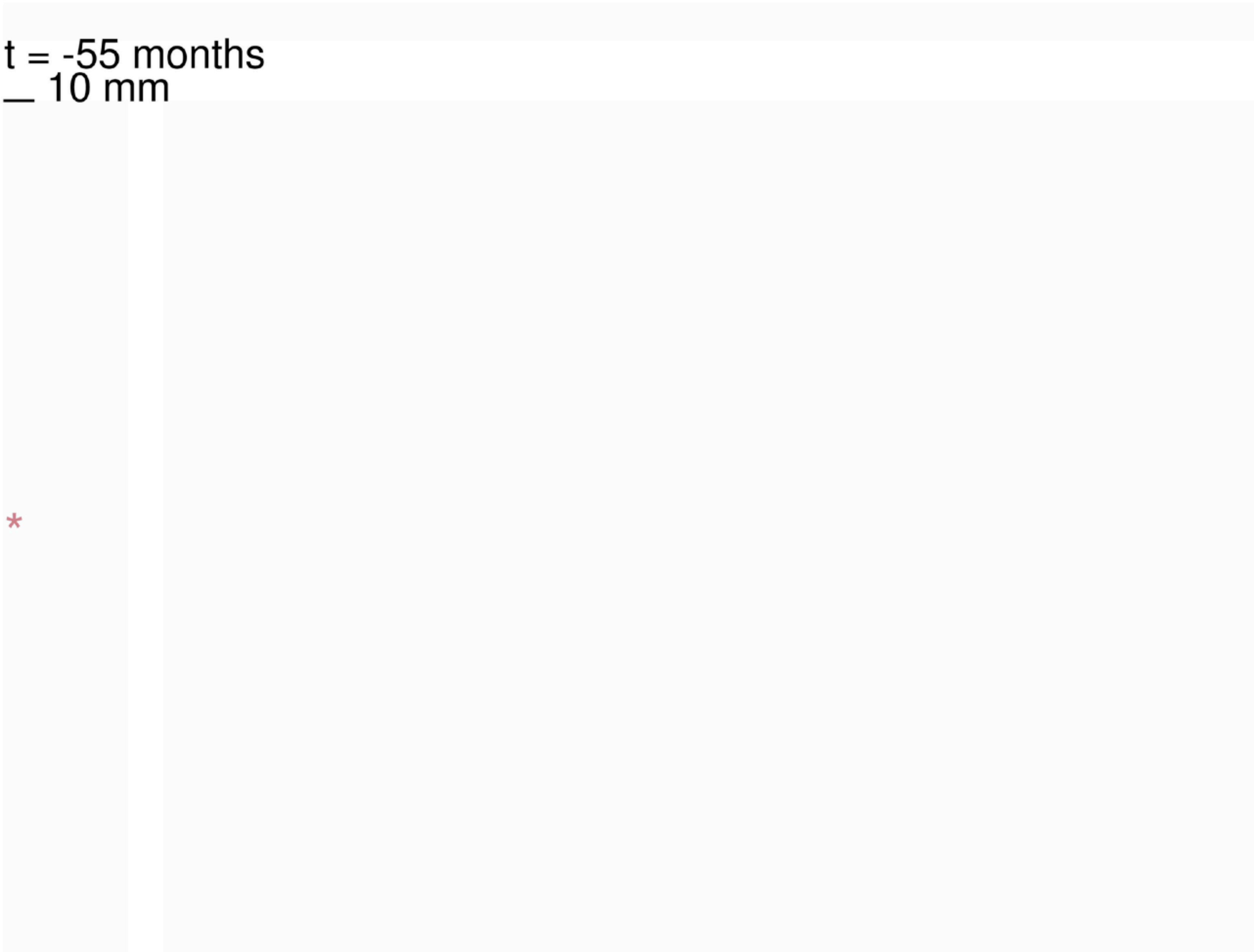
Objective function

Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

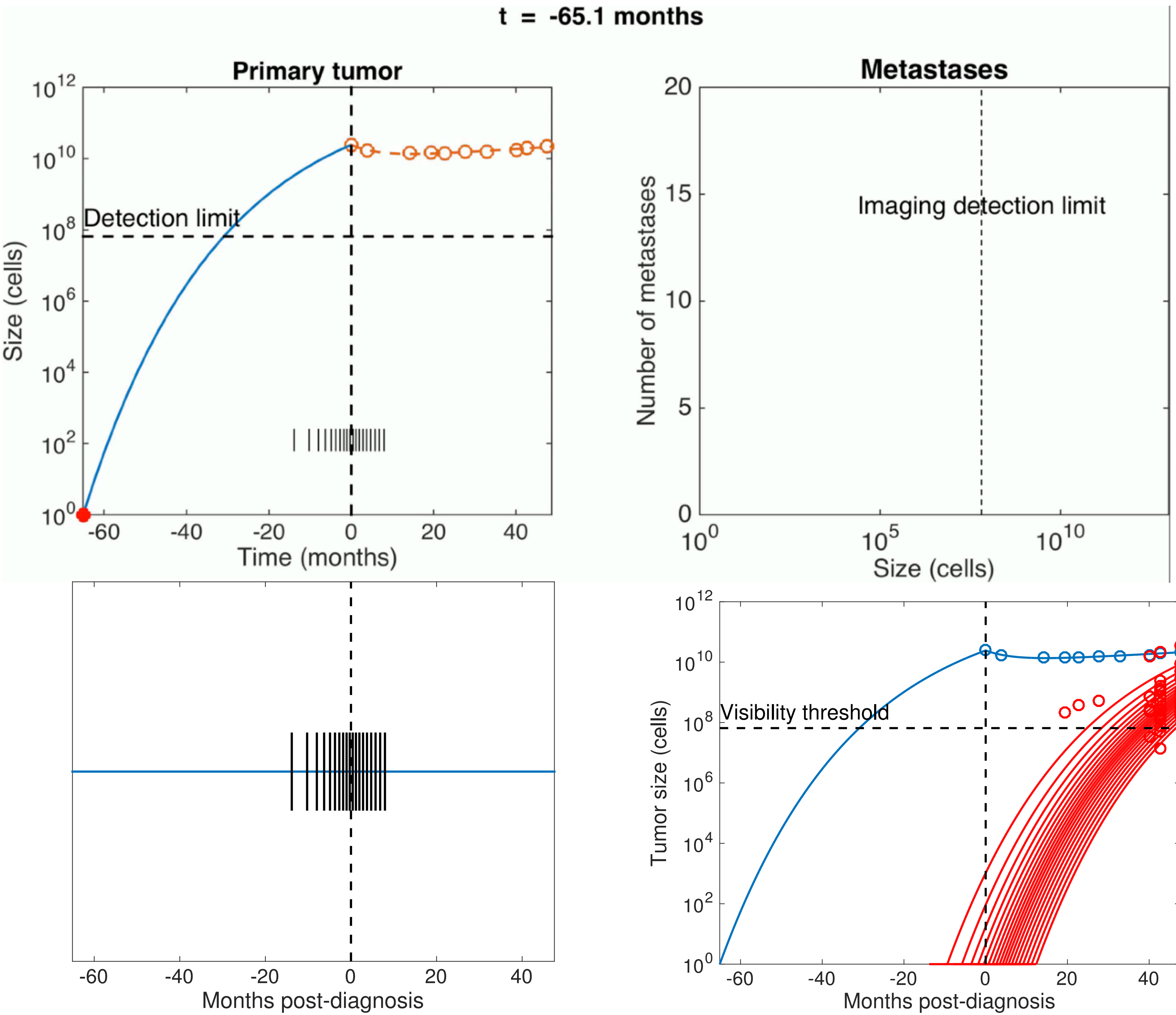
Dormancy estimated to 133 days ± 4.2%



Bilous et al. (Benzekry), biorXiv, 2018



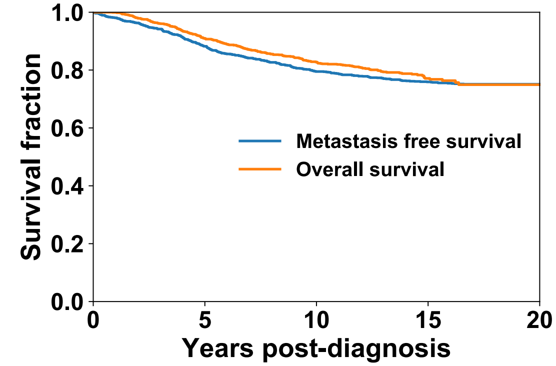
Bilous et al. (Benzekry), biorXiv, 2018



t = -65.1 months
Primary tumor
Size (cells)
Detection limit
Time (months)
Metastases
Number of metastases
Imaging detection limit
Size (cells)
Months post-diagnosis
Tumor size (cells)
Visibility threshold
Months post-diagnosis

Clinical application - Metastatic relapse in breast cancer

Clinical data of individual breast metastatic relapse



K = **25** features

n =1057 patients (**642** w/o adj)

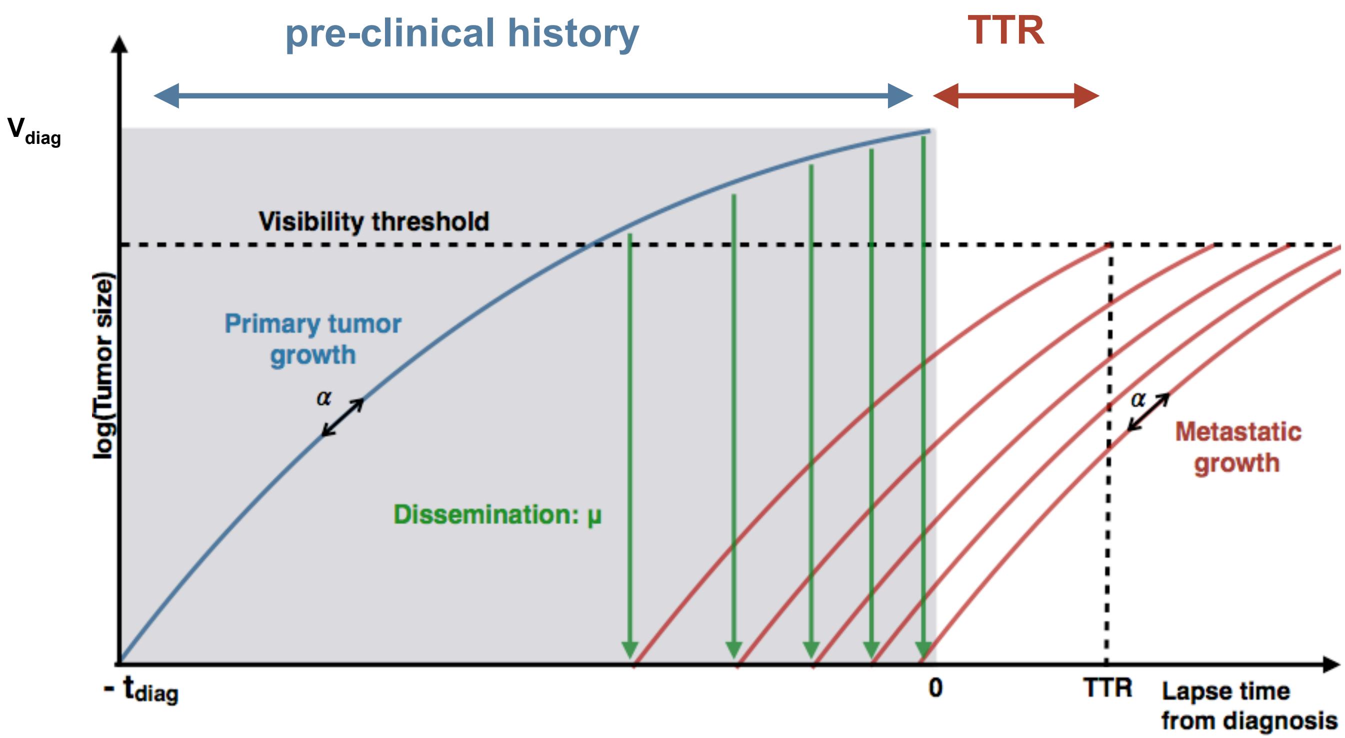
menopausal_status	ER	PR	Ki67	HER2	HER2_intensity	CK56	EGFR	VIM	ALDH1
Post-ménopause	20	0	0	0	0	0	0	0	0
Ménopause	40	95	8	0	0	0	0	0	0
Activité génitale	87	10	26	0	0	0	0	80	0
Post-ménopause	100	100	8	0	0	0	0	0	0
Post-ménopause	0	0	16	82	+++	0	0	0	0
Activité génitale	100	95	12	0	0	0	0	0	1
Activité génitale	56	100	17	0	0	0	0	0	0
Activité génitale	57	85	23	100	+++	0	0	0	0
Post-ménopause	80	5	20	0	0	0	0	0	0
Post-ménopause	0	0	15	100	+++	0	5	0	0
Post-ménopause	100	80	10	0	0	0	0	0	0
Post-ménopause	30	0	5	0	0	0	0	0	0
Post-ménopause	0	0	15	40	+++	0	0	0	0
Ménopause	0	80	8	0	0	0		0	0
Post-ménopause	0	0	27	0	0	0	30	0	1
Post-ménopause	0	0	56	0	0	80	60	100	0
Activité génitale	50	92	2	1	+	0	0	0	0
Post-ménopause	0	47	5	0	0	0	0	80	0
Post-ménopause	65	0	10	0	0	0	0	60	0
Post-ménopause	100	50	11	0	0	0	0	0	0
Ménopause	20	100	0	0	0	0	0	0	0
Activité génitale	90	6	5	0	0	0	0	0	0
Post-ménopause	100	3	5	0	0	0	0	0	0
Activité génitale	0	0	6	0	0	0	0	0	0
Ménopause	80	100	5	0	0	0	0	0	0
Post-ménopause	100	85	25	0	0	0		0	0
Post-ménopause	10	45	11	13	+++	0	0	0	0
Post-ménopause	66	1	2	40	++	0	0	0	0

outcome

date_metastatic_relapse	date_death_or_loss
854	*0*
censored	
1999-02-04 00:00:00	1998-04-26 00:00:0
	1999-01-06 00:00:0
	1993-10-21 00:00:0
	2004-06-15 00:00:0
1990-09-04 00:00:00	2006-03-21 00:00:0
1993-02-08 00:00:00	2002-04-05 00:00:0
1999-12-15 00:00:00	2006-11-23 00:00:0
	1997-11-02 00:00:0
	2006-09-15 00:00:0
1995-03-08 00:00:00	2003-03-29 00:00:0
	2003-12-02 00:00:0
1990-04-06 00:00:00	1990-10-20 00:00:0
1994-11-02 00:00:00	2003-10-14 00:00:0
	2004-11-19 00:00:0
	2006-09-30 00:00:0
	1991-07-31 00:00:0
	1995-07-05 00:00:0
	2005-12-08 00:00:0
	2005-05-23 00:00:0
	2007-09-06 00:00:0
	2006-09-06 00:00:0
	2001-02-09 00:00:0
	2005-07-23 00:00:0
	1993-08-12 00:00:0
	1995-01-01 00:00:0
	1993-02-08 00:00:0

Institut Bergonié, Bordeaux, FR

Mechanistic modeling of time to relapse



- Number of metastases with size larger than the visible size V_{vis} (= 0.5 cm)

$$N_{vis}(t) = \int_{V_{vis}}^{+\infty} \rho(t,v)dv = \int_0^{t-\tau_{vis}} d(V_p(t))dt$$

τ_{vis} = time to reach V_{vis}

- Time to relapse (TTR) defined as the time elapsed from diagnosis to the appearance of a first visible metastasis

$$TTR = \inf\{t > 0 : N_{vis}(t_{diag} + t) \geq 1\}$$

- Parameter β fixed such that carrying capacity = 10^{12} cells

Nicolò et al., in preparation, 2019

Mixed-effects statistical model

$$\ln\left(T^i\right) = \ln\left(TTR\left(V^i_{diag};\alpha^i,\mu^i\right)\right) + \varepsilon^i, \quad \varepsilon^i \sim \mathcal{N}(0,\sigma^2)$$

(Observation model)

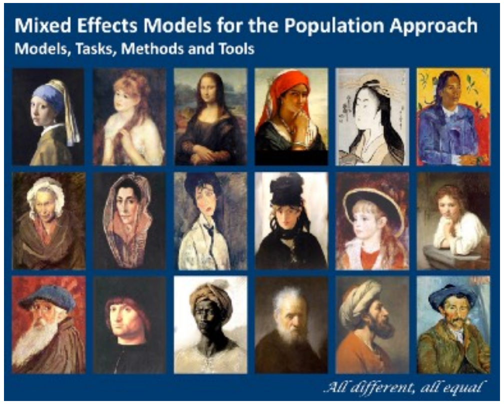
$$S\left(t|\alpha^i,\mu^i\right) = \mathbb{P}\left(T^i > t|\alpha^i,\mu^i\right)$$

Survival function to account for censoring in the likelihood

$$\ln\left(\alpha^i\right) = \ln\left(\alpha_{pop}\right) + \eta^i_\alpha, \quad \eta^i_\alpha \sim \mathcal{N}(0,\omega^2_\alpha)$$
$$\ln\left(\mu^i\right) = \ln\left(\mu_{pop}\right) + \eta^i_\mu, \quad \eta^i_\mu \sim \mathcal{N}(0,\omega^2_\mu)$$

fixed effects

random effects

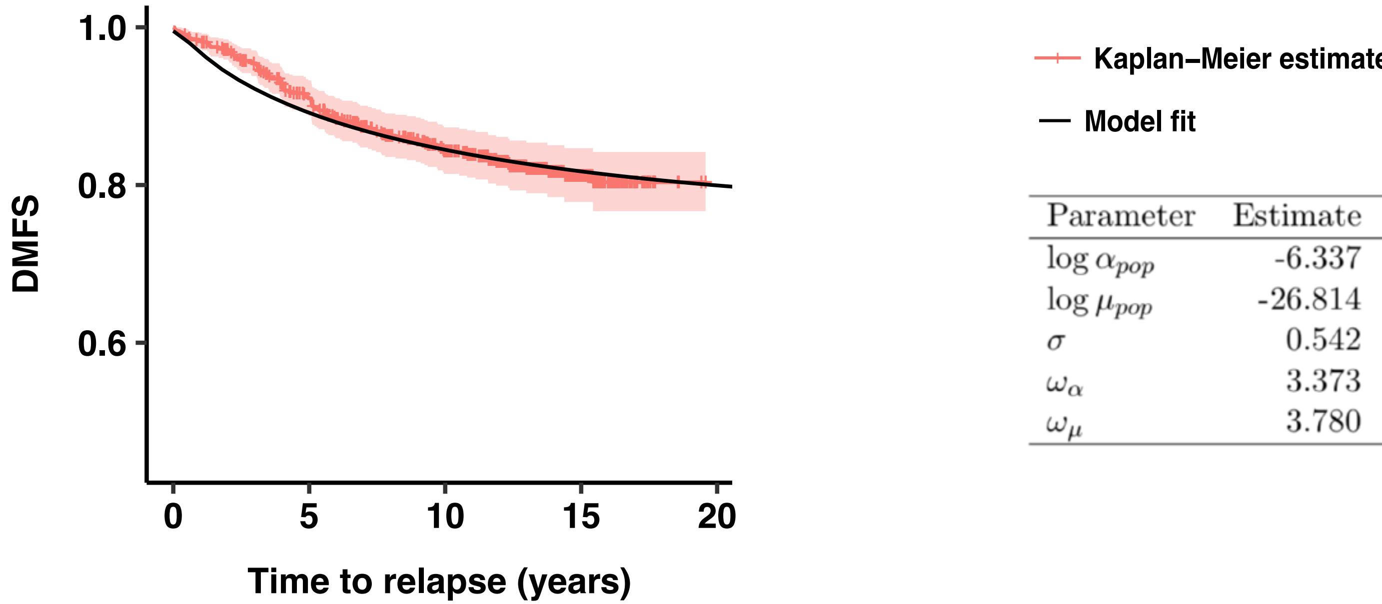


Lavielle, CRC press, 2014

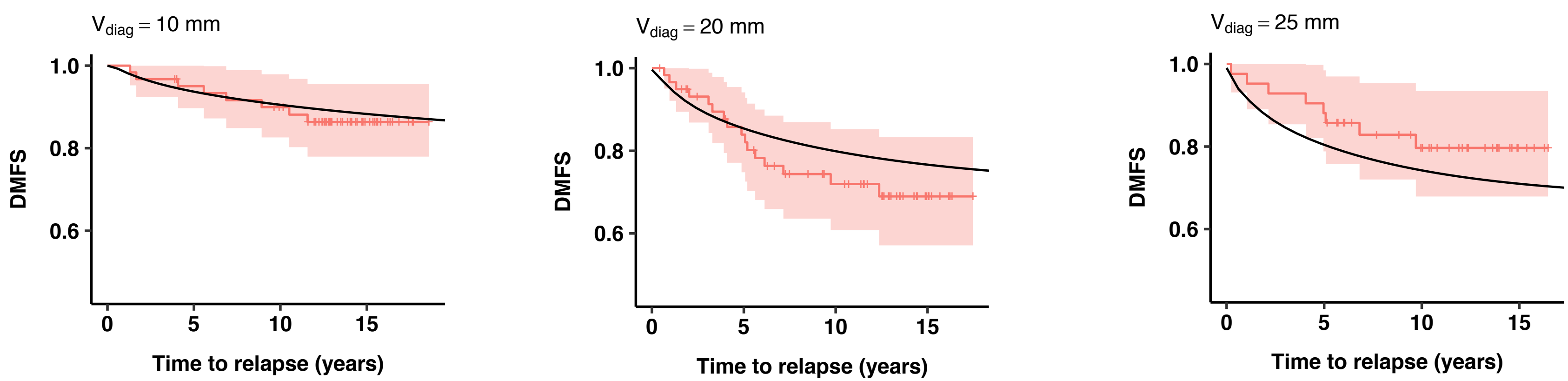
Likelihood maximization performed using the *saemix* R package (SAEM algorithm)

Comets, Lavenu, Lavielle, J Stat Softw, 2017

Descriptive power: fit to the data



Parameter	Estimate	r.s.e. (%)
$\log \alpha_{pop}$	-6.337	12.635
$\log \mu_{pop}$	-26.814	3.683
σ	0.542	28.409
ω_{α}	3.373	36.435
ω_{μ}	3.780	15.876



Nicolò et al., in preparation, 2019

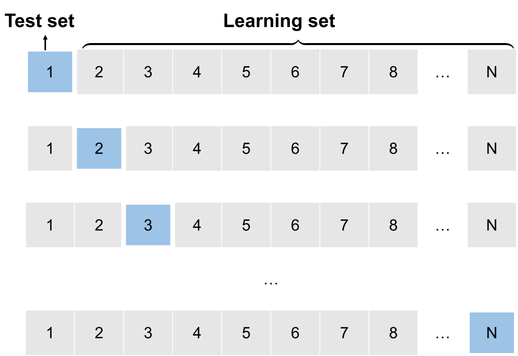
Predictive power: covariates

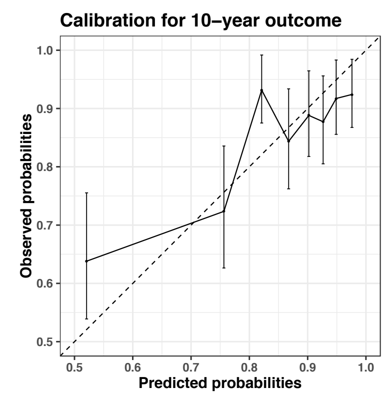
$$\ln\left(\mu^i\right) = \ln\left(\mu_{pop}\right) + \beta_\mu^T \mathbf{x}_\mu^\mathbf{i} + \eta_\mu^i, \quad \eta_\mu^i \sim \mathcal{N}(0, \omega_\mu^2)$$

$$\ln\left(\alpha^i\right) = \ln\left(\alpha_{pop}\right) + \beta_\alpha^T \mathbf{x}_\alpha^\mathbf{i} + \eta_\alpha^i, \quad \eta_\alpha^i \sim \mathcal{N}(0, \omega_\alpha^2)$$

Parameter	Estimate	r.s.e. (%)	p-value
$\log \alpha_{pop}$	-8.883	10.151	
$\beta_{\text{Ki67},\alpha}$	0.086	27.376	$2.59 \cdot 10^{-4}$
$\beta_{\text{HER2},\alpha}$	0.029	42.833	0.020
$\beta_{\text{CD44},\alpha}$	0.011	60.816	0.1
$\beta_{\text{TRIO},\alpha}$	0.016	58.119	0.085
$\log \mu_{pop}$	-26.342	3.696	
$\beta_{\text{EGFR},\mu}$	0.039	47.527	0.035
σ	0.606	23.104	
ω_α	2.062	22.715	
ω_μ	3.563	16.759	

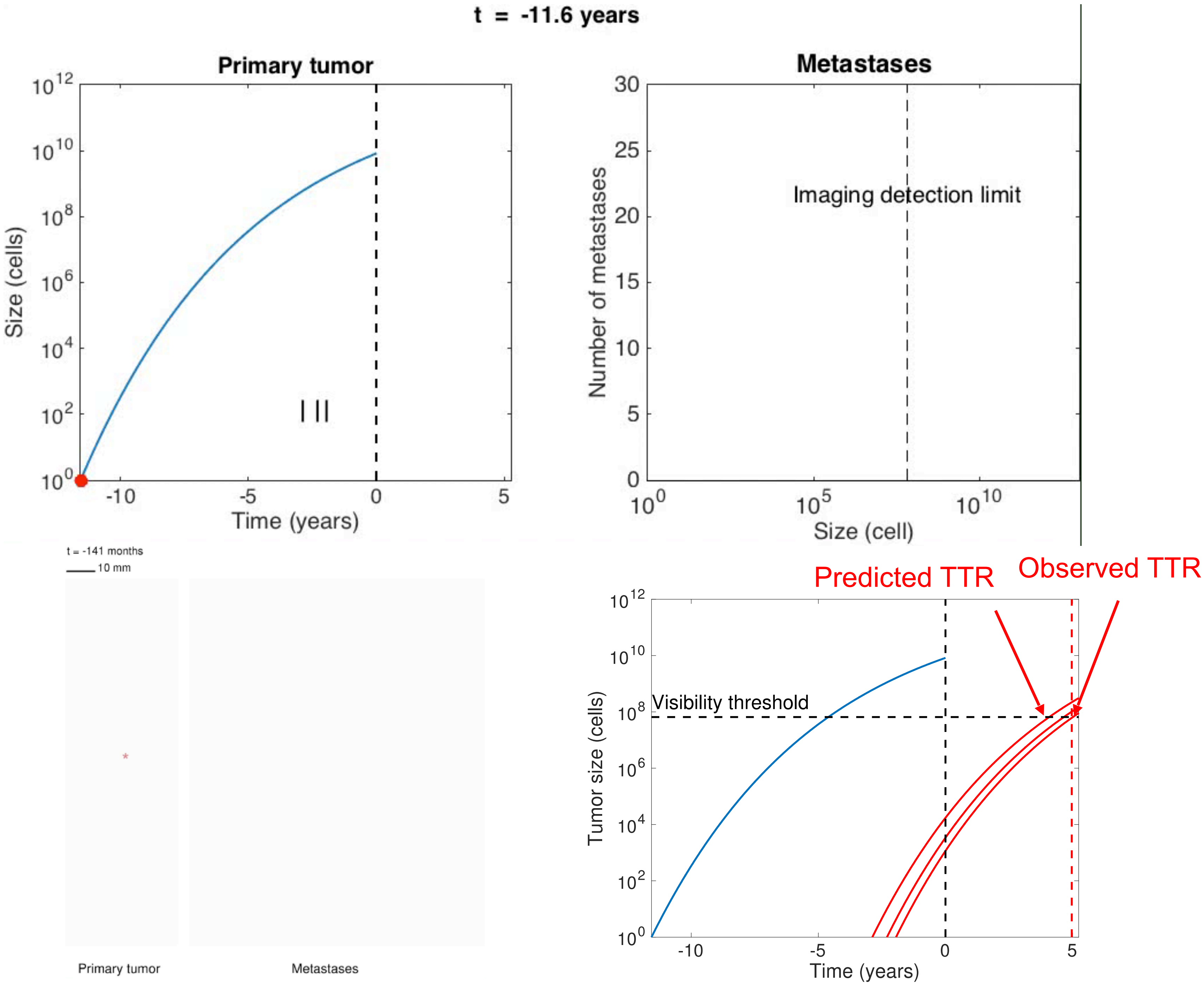
c-index = 0.62 (10-folds cross-validation)



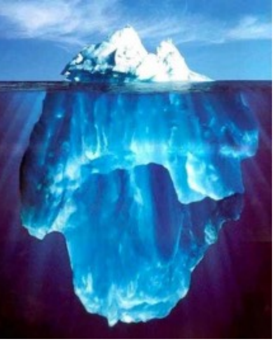


Patient ID	Tumor size (mm)	Ki67	HER2	CD44	TRIO	EGFR	Observed TTR (cens)	Predicted TTR	Prediction error (days)
47	20	32	100	0	0	50	739 (1)	447	292
255	25	1	60	90	60	0	1812 (1)	1609	203
143	18	60	0	50	0	0	2798 (1)	434	2364
12	10	20	0	23	0	0	5970 (0)	$+\infty$	-

Nicolò et al., in preparation, 2019



t = -11.6 years
Primary tumor
Size (cells)
Time (years)
Metastases
Number of metastases
Imaging detection limit
Size (cell)
t = -141 months
10 mm
Primary tumor
Metastases
Predicted TTR
Observed TTR
Visibility threshold
Tumor size (cells)
Time (years)

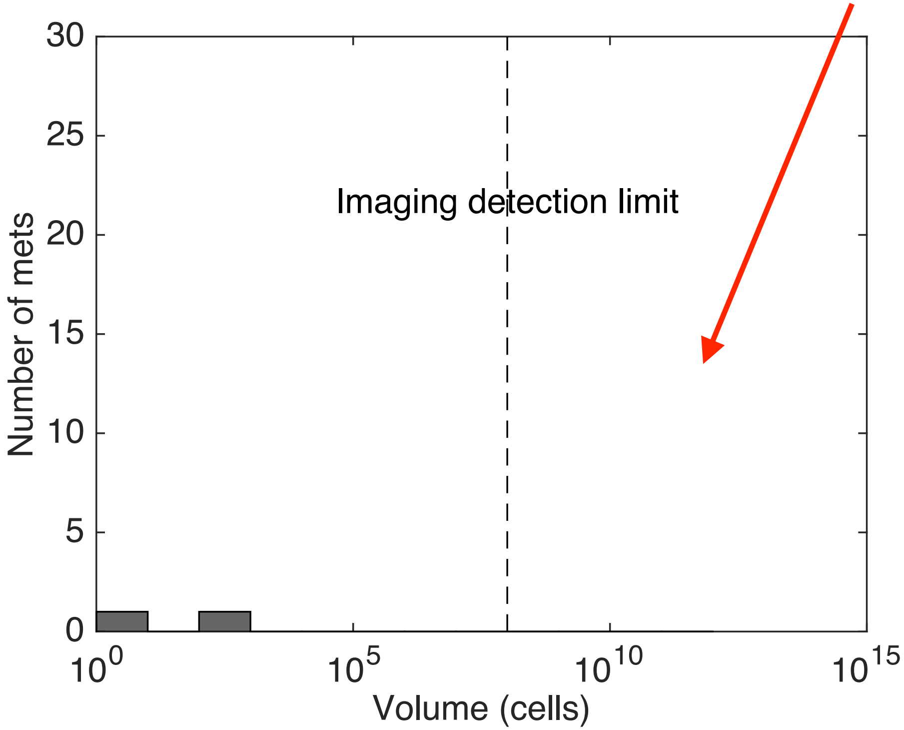


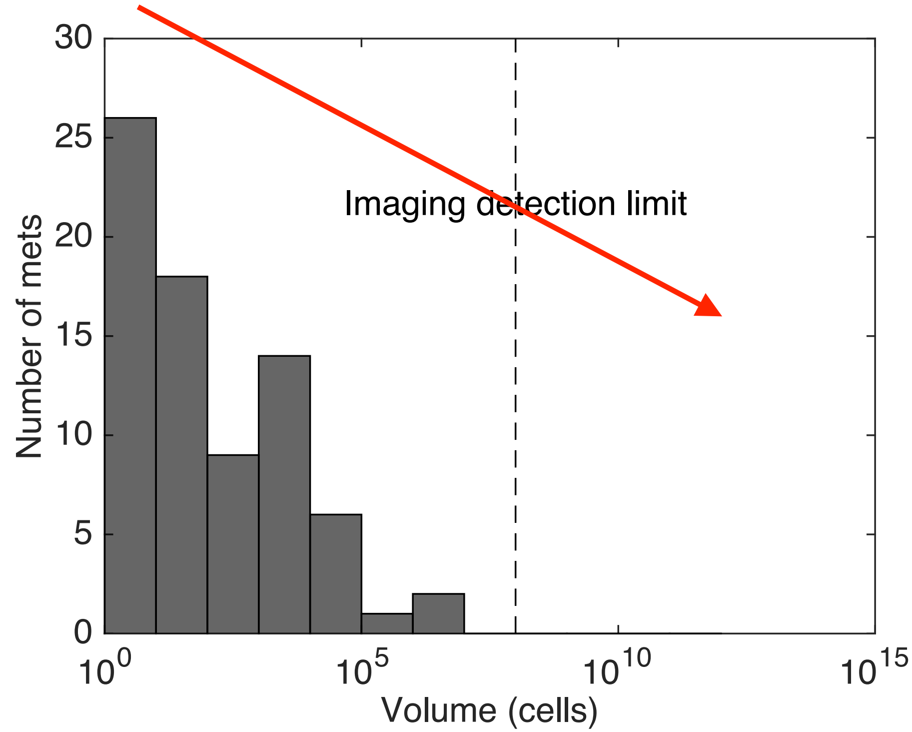
Diagnosis personalization

Virtual patient with median μ

Nothing visible

Virtual patient with large μ (90th prct)





Breast cancer patient with primary tumor of 4.32 cm

Chemotherapy personalization

Toward taking into account inter-individual variability

- 10 virtual patients with breast cancer detected at stage **T1N0M0**. Size of the tumor at detection: 1 gram.
- Chemotherapy : 6 cycles of 21 days (75mg of DTX and 100mg d'EPI) *Viens & al., J. Clin. Onc. 2001*
- Number of visible metastases (> 10^8 cel.) 5 years after the end of the treatment

Adapt the number of cycles to each patient

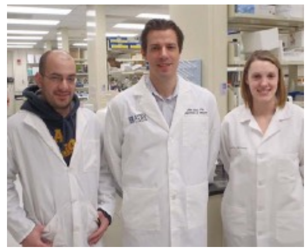
μ	Protocole de Viens		
	6 cycles 126 days	9 cycles 189 days	12 cycles 252 days
1.3×10^{-7}	**1**	0	$\star$
2.7×10^{-7}	**2**	1	0
4.0×10^{-7}	**3**	2	1
6.1×10^{-7}	**5**	4	3

Barbolosi, Verga, 2011

Acknowledgements

Biology

- Preclinical data of ortho-surgical animal models of metastases



✴J. Ebos ✴A. Tracz

✴M. Mastri

Roswell Park Cancer Institute, Buffalo, NY, USA

- Beva + cytotoxics study

SMARTc
SIMULATION MODELING ADAPTIVE RESPONSE FOR THERAPEUTICS IN CANCER

Dr. J. Ciccolini

Clinic

- Brain metastasis from lung tumors

✴F. Chomy **Bergonié Institute, Bordeaux, FR**

✴F. Barlesi

✴X. Muracciole

AP-HM, Marseille, FR

Modeling

✴C. Nicolò

✴D. Barbolosi


That's all Folks!
Thanks for listening!